REMARKS

With entry of this amendment, claims 1-50 are pending in the application. By this amendment, claims 1, 3-7, 9-13, 16-20, 22, 23, 28-30, 32-34, 36, 37, 39, 41-45, 47, 48, and 50 have been amended and claims 2, 14, 15, 27, 35, and 40 have been cancelled, without prejudice, for clarity in accordance with the Office's suggestions, and to place the application in better condition for Appeal or allowance. A Request for Continued Examination (RCE) and Petition for Extension of the Appeal period for two months, along with the appropriate fees, are filed herewith. All of the amendments herein are fully supported by the specification, and no new matter has been added to the application. Entry of these amendments and reconsideration of the application is earnestly solicited.

Compliance of Information Disclosure Statement with 37 CFR 1.98(a)(1)

The Office requests that Applicant file a Supplemental Information Disclosure Statement including certain references not listed on the IDS filed April 1, 2002. It is unclear from the record which references are sought to be added. Are the requested references those cited by the Examiner as prior art in the application? The Examiner is invited to call Applicant's representative below to clarify which references should be included in the proposed Supplemental IDS.

Patentability Under 35 U.S.C. § 112, first paragraph

Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement. In particular, the Examiner recognizes that the claims are enabling for treatment of cancer [Office Action at p. 8], but asserts that the specification is not fully enabling for prophylaxis, or prevention, of cancer. In this context, the Examiner principally contends that the art is poorly developed, and that cancer prophylaxis is highly unpredictable.

Without acceding to the merits of the rejection, Applicant notes that the rejection is rendered moot by amendment of the claims herein. In particular, the claims have been amended to clarify that the subject methods are limited to "[a] method of treatment of breast cancer." Moreover, the breadth of the claims has been further clarified by deletion of the term "other long-acting oxytocin analogues"—thereby limiting the subject active agent to carbetocin and its equivalents.

Subject matter thus withdrawn from the application is not relinquished by this Amendment, and Applicant reserves the right to pursue this subject matter in a related application.

In view of the foregoing, the rejection of claims 1-38 under 35 U.S.C. 112, first paragraph is respectfully submitted to be overcome.

Claims 13-25 and 34-38 are rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement. In particular, the Examiner recognizes that the claims are enabling for treatment of obsessive-compulsive disorder (OCD) [Office Action at p. 14], but asserts that the specification is not fully enabling for prophylaxis of OCD, or for treatment or prevention of other psychiatric disorders. In this context, the Examiner also principally contends that the art is poorly developed, and that prophylaxis of OCD and other psychiatric disorders is highly unpredictable.

Without acceding to the merits of the rejection, Applicant notes that the rejection is rendered moot by amendment of the claims herein. In particular, the claims have been amended to clarify that the subject methods are limited to "[a] method of treatment of obsessive compulsive disorder." Moreover, the breadth of the claims has been further clarified by deletion of the term "other long-acting oxytocin analogues"—thereby limiting the subject active agent to carbetocin and its equivalents.

Subject matter thus withdrawn from the application is not relinquished by this Amendment, and Applicant reserves the right to pursue this subject matter in a related application.

In view of the foregoing, withdrawal of the rejection of claims 13-25 and 34-38 under 35 U.S.C. 112, first paragraph is earnestly solicited.

Rejections under 35 U.S.C. § 103

Claims 1-12 and 26-33 and 39-50 are rejected under 35 U.S.C. § 103 as allegedly unpatentable over Harris et al. U.S. Patent No. 5,482,931 in view of Cassoni et al.

Harris et al. is cited for allegedly disclosing "nasal administration of the preferred pharmaceutical composition containing carbetocin as well as other analogs of oxytocin, (see column 2, lines 47-55)." The Examiner further asserts that "Harris et al. expands on this nasal

composition of carbetocin by providing motivation to use the nasal composition for the management of diseases and abnormal conditions, (cited from column 3, lines 25-29).

Cassoni et al. is relied upon for allegedly disclosing "the administration of oxytocin as well as oxytocin analogues, which show receptor-mediated inhibitory effects on the proliferation of human breast carcinoma cells." On this basis, the Examiner concludes that Cassoni et al. provide the skilled artisan with the motivation to treat breast cancer with oxytocin and its analogues, (see page 471, column 2, 4th paragraph).

Based on these alleged teachings, the Examiner contends that "[t]he skilled artisan would have been motivated to utilize the preferred pharmaceutical peptide of carbetocin, as taught by Harris et al., as a treatment of breast cancer due to the fact that carbetocin is a structural analogue of oxytocin, (see column 2, lines 47-55 of Harris et al.) when the prior art reference of Harris et al. is combined with the teachings of Cassoni et al."

Applicant respectfully traverses the foregoing grounds of rejection as presented by the Examiner, and submit that the Harris et al. and Cassoni et al. references, taken alone and viewed in combination, fail to teach or suggest the subject matter of the claims presented for review.

As an initial point, Applicant's claims as amended herein are directed to methods and compositions for treatment of breast cancer in a mammalian patient employing "a therapeutically effective amount of carbetocin in a pharmaceutically acceptable carrier sufficient to inhibit growth of breast cancer in said patient." As such, the amended claims do not read on any oxytocin analog, nor on prophylaxis, or prevention, of breast cancer.

Examining first the Harris et al. reference, Applicant respectfully submits that this reference has been misconstrued by the Office. In particular, the reference is actually directed to methods and compositions to inhibit "degradation of desmopressin by hydrolytic and/or oxidative processes", and to ameliorate the problem of adsorption found "with dilute solutions of peptides." [col. 1, ll. 34-41]. The focus of the disclosure is the use of "a quaternary amine preservative or disinfectant" as a preservative that has "the unexpected ability to prevent adsorption of small and medium size peptide components from adhering to container walls." [col. 2, ll. 41-46]. This invention is generally disclosed as being applicable to all "small and medium-size peptides. The principal subject of this disclosure (and the only subject of actual working examples) is desmopressin. The reference only vaguely and prophetically asserts that other "peptides" or "peptide analogs" for which the invention may be applicable include

vasopressin, oxytocin, terlipressin, atosiban, carbetocin, and troptorelin. Notably, these other peptide candidates, like the broad, speculative group of all "small and medium size peptide components", are only mentioned in the context of their amenability for preservation and adsorption inhibition using the disclosed quarternary ammine preservative. [col. 2, ll. 47-55].

As such, the Harris et al. reference teaches nothing about a structure-function relationship between carbetocin and oxytocin. The mention of carbetocin is entirely prophetic, and incidental. Most importantly, any structure-function analogy that may be implied between oxytocin and carbetocin based on this reference would necessarily be limited to the predicted behavior of these discrete compounds with respect to preservation and adsorption inhibition following their admixture with a quarternary ammine preservative. These limited teachings are clearly inapposite to the claimed invention and add nothing to the teachings of Cassoni et al., contrary to the Examiner's assertions. No sound scientific evidence can be gleaned from this reference with regard to other predicted activities of carbetocin as an oxytocin analog, particularly as an effective compound within Applicant's compositions and methods for treating cancer.

In a similar context, the Harris et al. reference provides no basis for suggesting the usefulness of carbetocin in any pharmaceutical formulation or method, much less in a composition or method that is effective for treating breast cancer. The passage relied upon by the Examiner as "motivation to use the nasal composition for the management of diseases and abnormal conditions" provides no detail whatsoever about the use of carbetocin for treating any specific disease or condition. On the contrary, when read in full context the cited passage reads:

> [T]here is also disclosed the use of an aqueous spray composition for the management of diseases and abnormal conditions that can be treated by nasal administration of small and medium-size peptides. (emphasis supplied).

This passage, if construed according to the Examiner's interpretation, would read on any small or medium peptide composition for treating any "diseases and abnormal conditions."

> [T]he vague 'basket' disclosure of possible uses in the [prior art] are unimportant. What is important is the fact that the utility discovered by the appellants is not disclosed in the prior art." In re Ruschig, 145 USPQ 274, 285 (CCPA 1965) (emphasis in original).

The Office's reliance upon Cassoni et al. as a secondary reference to Harris et al. is equally misplaced. As noted above, the Examiner construes the teachings of Cassoni et al. as allegedly applying to "oxytocin as well as oxytocin analogues", which the Examiner asserts to include carbetocin. However, carbetocin is nowhere even mentioned in the Cassoni et al. disclosure. In fact, the only "oxytocin analogue" discussed in the reference is F314—a compound distinct from carbetocin. Whereas F314 is disclosed by Cassoni et al. as inhibiting "oestrogen-induced cell growth" in human breast cancer cells, the reference provides no scientific basis for a functional prediction concerning the activity of carbetocin, particularly within Applicant's novel methods and compositions.

On the contrary, Cassoni et al. teach away from such a predicted activity for carbetocin in its characterization of useful oxytocin (OT) analogues. In particular, the reference states the following characterization with respect to F314 and other OT analogues:

> We tested the hypothesis that OT and OT analogues (synthetic peptides binding to OT receptors but devoid of contractile activity) may exert the same effect on the growth of breast cancer cells. (underscore added).

This definition of an effective oxytocin analogue within the limited assays conducted by Cassoni et al. expressly excludes and distinguishes carbetocin from F314 and any other useful analogues contemplated by the authors. Notably, Applicant's specification clearly identifies carbetocin as having "contractile activity" as one of its defining characteristics, as follows:

> **One such analog, carbetocin** (1-butanoic acid-2-(O-methyl-L-tyrosine)-1-carbaoxytocin, or, alternatively, deamino-1 monocarba-(2-O-methyltyrosine)-oxytocin [d(COMOT)]) is a long-acting synthetic oxytocin analog which **exhibits both uterotonic and milk let-down inducing activities** (Atke et al., Acta Endocrinol. 115:155-160, 1987; Norstrom et al., Acta Endocrinol. 122:566-568, 1990; Hunter et al., Clin. Pharmacol. Ther. 52:60-67, 1992; Silcox et al., Obstet. Gynecol. 82:456-459, 1993; Vilhardt et al., Pharmacol. Toxicol. 81:147-150, 1997; Boucher et al., J. Perinatology 18:202-207, 1998). (See, page 5, line 32 to page 6, line 7; emphasis supplied).

Because Cassoni et al. define an OT analogue as a compound that binds OT receptors but is "devoid of contractile activity", carbetocin must be considered to be expressly excluded from the teachings of the reference. Moreover, because Cassoni et al. disclose that F314 is an effective OT analog for inhibiting oestrogen-induced cell growth, and in view of the fact that

F314 differs from carbetocin in one of the most fundamental activities (i.e., contractile activity), the reference must be considered to actually teach away from Applicant's invention.

The foregoing evidence and authority clearly demonstrate that the combined teachings of Harris et al. and Cassoni et al. fail to teach or suggest the subject matter of Applicant's claims as currently presented for review. Additional evidence of record further clarifies the deficiencies of these references, which fail to support the instant rejection.

Considering a broader series of studies by Cassoni et al., the authors reported that oxytocin and F314 inhibits proliferation of human hormone-dependent MCF7 and hormone-independent MDA-MB231 breast cancer cells *in vitro* and enhances the known inhibitory effect of tamoxifen on estrogen-dependent MCF7 cells and TS/A (Cassoni et al., Virchows Archiv. 425:467-472, 1994; Cassoni et al., Int. J. Cancer 66:817-820, 1996; Cassoni et al., Int. J. Cancer 72:340-344, 1997; Sapino et al., Anticancer Res. 18:2181-86, 1998). Based on the accumulated data from these reports, the Cassoni et al. propose that oxytocin may mediate a spectrum of different cellular responses, in different signal-transduction systems, in cells with different phenotypes, and in combination with other mammotrophic hormones through yet undefined mechanisms and pathways. The record is thus clear, and consistent with the Examiner's own views with regard to enablement of cancer prophylaxis methods, that the art is poorly developed and unpredictable as it pertains to the possible effects of oxytocin, various oxytocin analogs, and other hormonal regulatory factors, on breast cell growth, differentiation and survival. This uncertainty is underscored by a number of conflicting reports about the nature and activity of oxytocin as a regulatory factor in breast cell development.

For example, Taylor et al., Cancer Res. 50:7882-7886, 1990, reported that oxytocin is mitogenic for estrogen-dependent MCF7 cells—an opposite conclusion to that rendered by the Cassoni research group in the series of reports discussed above. The mitogenic activity of oxytocin observed by Taylor and coworkers was shared by another peptide hormone, vasopressin. However, vasopressin was observed to be mitogenic for MCF7 cells only at low doses, and to exert an opposite, anti-proliferative effect on these same cells at higher doses. In a separate report Sapino et al. (Anticancer Res. 18:2181-86, 1998) stated that oxytocin exerts an independent "trophic effect" on breast myoepithelial cells that induces their proliferation and differentiation. In yet another conflicting study, Ito and coworkers (Endocrinology 137:773-779, 1996) report that "the effects of OT (oxytocin) on the growth of cultures breast cancer cells are

inconsistent in the short term", and that available data suggest "that OT does not influence the morphological differentiation of the cancer cell. These collective reports clarify and emphasize the many deficiencies of the prior art with respect to providing insight and guidance about the potential utility of carbetocin for successful treatment of breast cancer as disclosed by Applicant.

In view of the foregoing, Applicant respectfully submits that the rejection of claims 1-12 and 26-33 and 39-50 under 35 U.S.C. § 103 as allegedly unpatentable over Harris et al. U.S. Patent No. 5,482,931 in view of Cassoni et al. has been overcome.

Claims 13-25 and 34-38 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Harris et al. of U.S. Patent No. 5,482,931 in view of Leckman et al. Harris et al. is cited for the same teachings noted above--namely for allegedly disclosing nasal administration of carbetocin and other analogs of oxytocin, and for "providing motivation to use the nasal composition for the management of diseases and abnormal conditions". Leckman et al. is relied upon for allegedly teaching administration of oxytocin to treat obsessive compulsive disorder, (see abstract and pages 723 and 724).

Applicant respectfully traverses the foregoing grounds of rejection as presented by the Examiner, and submit that the Harris et al. and Leckman et al. references, taken alone and viewed in combination, fail to teach or suggest the subject matter of the claims presented for review.

As discussed in detail above, the Harris et al. reference teaches nothing about a structure-function relationship between carbetocin and oxytocin. The mention of carbetocin in this reference is entirely prophetic, and incidental. Any structure-function analogy that may be implied between oxytocin and carbetocin based on this reference would necessarily be limited to the compounds' predicted behavior with respect to preservation and adsorption inhibition in the presence of a quarternary ammine preservative. These teachings are speculative as presented and wholly inapposite to the instantly claimed invention. There is no evidence to be gleaned from this reference with regard to predicted activities of carbetocin as an oxytocin analog, particularly as an effective compound within Applicant's compositions and methods for treating cancer.

As also discussed in detail above, the Harris et al. reference provides no basis for suggesting the usefulness of carbetocin in any pharmaceutical formulation or method, much less in a composition or method that is effective for treating breast cancer. The passage relied upon by the Examiner as "motivation to use the nasal composition for the management of diseases and

abnormal conditions" provides no detail about the use of carbetocin for treating any specific disease or condition. On the contrary, the broad passage cited by the Examiner, if construed as the Office asserts, would read on any small or medium peptide composition for treating any "diseases and abnormal conditions." Such "basket" disclosures are inadequate as a basis for asserting unpatentability In re Ruschig, 145 USPQ 274, 285 (CCPA 1965).

Turning now to the secondary references, Boer et al. and Leckman et al., Applicant believes that both references actually teach away from the instantly claimed subject matter. Notably in this context, Boer et al. (at page 1085, paragraph bridging columns 1 and 2) reported that they observed:

> no reduction in the number of compulsive behaviors . . . neither in the oxytocin group, nor in the placebo group. The present results indicate that oxytocin at the dosage used in this study, does not possess anticompulsive properties. IN addition, no significant reductions in the associated anxious and depressive symptomology were observed. (emphasis supplied).

Thus, at two different dosages administered to patients, there were reportedly no anticompulsive properties of oxytocin observed.

Leckman et al. similarly undermine the Office's position and teach directly away from Applicant's claimed invention. In particular, these authors unambiguously state that:

> [A] role for oxytocin in the pathogenesis of obsessive compulsive disorder is meager and has mostly focused on systematically administered oxytocin's equivocal value as a therapeutic agent. The authors further state that oxytocin delivered via intravenous, intraperitoneal or intranasal routes is an ineffective therapy. [page 727, 1st paragraph].

Considering the foregoing facts and authority, Applicant respectfully submits that the proposed combination of references, Harris et al., Boer et al., and Leckman et al., fails to collectively teach or suggest Applicant's claimed compositions and methods for treating OCD. Harris et al. fails to teach, and may be considered to teach away from, a reliable structure-function parity between oxytocin and carbetocin for any treatment method, much less for an effective OCD treatment method. Boer et al. and Leckman et al. similarly fail to comprehend a useful identity of structure function between oxytocin and carbetocin for treating OCD. In fact, both references fail to teach away from using any oxytocin analog within Applicant's claimed compositions and methods.

Claims 26-37 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Harris et al. of U.S. Patent No. 5,482,931. The teachings of Harris et al. as asserted by the Office, and the several deficiencies of this references noted by the Applicant, are addressed in detail, above. The central contention of the Examiner that Harris et al. teach nasal administration of carbetocin, and the use of such formulations and methods for "the management of diseases and abnormal conditions", is believed to be refuted by the evidence and authority presented above. Accordingly, Applicant respectfully urges that this rejection also be withdrawn.

Claims 11, 12, 32, 49 and 50 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Harris et al. of U.S. Patent No. 5,482,931 in view of Cassoni et al. and Windholz, Ed. of The Merck Index, 10th Edition. Harris et al. and Cassoni et al. are relied on, as above, for allegedly disclosing administration of carbetocin, asserted to have "receptor-mediated inhibitory effects on the proliferation of human breast carcinoma cells." The Merck Index is cited for allegedly disclosing the usefulness of tamoxifen to treat breast cancer.

As discussed in detail above, there is no sound scientific basis to assert that Harris et al. discloses administration of carbetocin effectively in any specific disease treatment composition or method. The subject reference is actually directed to methods and compositions to inhibit "degradation of desmopressin by hydrolytic and/or oxidative processes", and to ameliorate the problem of adsorption found "with dilute solutions of peptides." Harris et al. teach nothing about a structure-function relationship between carbetocin and oxytocin, and the single mention of carbetocin in the disclosure is wholly prophetic, and incidental.

As also noted above, Cassoni et al. expressly excludes carbetocin from the definition of a functional oxytocin "analogue", which are defined as "synthetic peptides binding to OT receptors but devoid of contractile activity". Applicant's specification and the numerous references cited therein clearly denote that carbetocin exhibits "contractile activity" as one of its defining characteristics. These combined references, therefore, cannot be fairly relied upon to support an obviousness rejection of the instantly claimed invention. Accordingly, withdrawal of the rejection of claims 11, 12, 32, 49 and 50 35 U.S.C. 103(a) over Harris et al. and Cassoni et al. is respectfully requested.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 425.455.5575.

Respectfully submitted,

Dated: November 10, 2003

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